REMARKS

Applicants have canceled claims 1-21, 25-26, and 36-37. Thus, claims 22-24, 27-29, 31-35, and 38-43 are pending. In light of the following remarks, Applicants respectfully request reconsideration and allowance of claims 22-24, 27-29, 31-35, and 38-43.

Restriction Requirement

Applicants acknowledge the Examiner's withdrawal of the restriction between Groups VII and VIII. Claim 43 has been restored to "original" status.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 22-24, 27-29, 33-35, and 39-43 under 35 U.S.C. § 102(b) as being anticipated by the Delaney *et al.* reference (Delaney and Langlands (1996) *The Breast* 5:53-54) as evidenced by U.S. Patent No. 5, 658,936 (the Kifor *et al.* reference).

Claims 22-24, 27-29, and 31-32 relate to methods for using a chloride channel blocking agent to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction. Claims 33-42 relate to methods for using a chloride channel blocking agent to modulate penile vascular tone in a mammal in need thereof. Claim 43 recites a method for treating erectile dysfunction.

The Examiner stated that the Delaney *et al.* reference teaches that a patient treated with tamoxifen exhibited significantly enhanced libido. The Examiner also stated that the Kifor *et al.* reference reports that an improvement in erectile function is defined as increased libido. The Examiner further stated that Applicants' recitation in the claims of a mechanism for modulating penile vascular tone does not represent a patentable limitation, and that tamoxifen has been previously used to obtain the same pharmacological effect (enhanced erection) that would result from the claimed method.

Applicants respectfully disagree. First, the Delaney *et al.* reference fails to anticipate the present claims. The Delaney *et al.* reference discloses that a male patient on a tamoxifen regimen had experienced increased libido during his course of treatment. At no point does the Delaney *et al.* reference disclose that the patient had compromised vascular tissue associated with erectile dysfuction, as recited in claims 22-24, 27-29, and 31-32. Further, at no point does

the Delaney *et al.* reference disclose that the patient was in need of modulated penile vascular tone as recited in claims 33-35 and 38-42, or was diagnosed with erectile dysfunction as recited in claim 43. While the Delaney *et al.* reference suggests that tamoxifen may have been the cause of the patient's increased libido, this reference fails to even suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction.

Second, the Delaney *et al.* reference fails to establish a causative link between tamoxifen treatment and increased libido. The reference discloses that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to the Delaney *et al.* reference, the patient began tamoxifen treatment in April 1993. Ten months later, in February 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding 6 months. As such, the onset of increased libido did not occur until the patient had been taking tamoxifen for about 4 months. Moreover, when the patient was reevaluated in January 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

The Delaney *et al.* reference does not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido. In addition, Delaney *et al.* did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. In fact, the authors of the Delaney *et al.* reference were unsure as to the cause of the increased libido, as they speculate that it may have been related to the relatively young age of the patient. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, the Delaney *et al.* reference discloses that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence. In fact, the Delaney *et al.* reference discloses that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, the Delaney

et al. reference clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Third, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Libido is a psychological phenomenon that is defined by the Merriam-Webster online dictionary as "[1]emotional or psychic energy that in psychoanalytic theory is derived from primitive biological urges and that is usually goal-directed; or [2]sexual drive." Erectile dysfunction is a physiological condition that is defined by the On-Line Medical Dictionary as "a consistent inability to sustain an erection sufficient for sexual intercourse." Copies of these definitions are attached hereto for the Examiner's convenience. Given these differences, increasing libido and modulating penile vascular tone to treat erectile dysfunction are likely accomplished by different mechanisms. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction.

The Kifor *et al.* reference is consistent with the above definitions when it states that improved erectile function can include "any enhancement of the ability of a subject to maintain an erection, induce or improve ejaculation, induce or improve orgasm, and increase libido." (See, column 7, lines 4-8 of the Kifor *et al.* reference.) Thus, an increase in libido may improve erectile dysfunction, but does not necessarily do so. As such, improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of the Delaney *et al.* reference to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited reference does not anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 22-24, 27-29, 33-35, and 39-43 under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 31, 32, and 38 under 35 U.S.C. §103(a) as being unpatentable over the Delaney *et al.* reference as applied to claims 22-24, 27-29, 33-35, and 39-43, and further in view of U.S. Patent No. 6,266,560 (the Zhang *et al.* reference) and Drug Facts and Comparisons (1997). The Examiner stated that while the Delaney *et al.* reference does not expressly teach the route of administration set forth in claims 32 and 38 or the further administration of the agents set forth in claim 31, Drug Facts and Comparisons teaches that tamoxifen is commercially available in oral form, while the Zhang *et al.* reference reports that vasodilators are useful for treatment of erectile dysfunction. Thus, the Examiner concluded that it would have been obvious to a person having ordinary skill in the art to administer tamoxifen orally. The Examiner also concluded that it would have been obvious to incorporate a vasodilator agent with tamoxifen because vasodilators are useful for treatment of erectile dysfunction.

Applicants respectfully disagree. Claims 31 and 32 depend from claim 22, and claim 38 depends from claim 33. Thus, these claims relate to methods for using a chloride channel blocking agent to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction, or to modulate penile vascular tone in a mammal in need thereof. As discussed above, the Delaney *et al.* reference discloses only that one male patient experienced increased libido during a portion of the time for which he was on a tamoxifen regimen. The Delaney *et al.* reference fails to disclose a causative link between tamoxifen treatment and increased libido. In fact, this reference teaches that tamoxifen treatment is more likely to result in reduced libido than increased libido. Moreover, the Delaney *et al.* reference does not suggest that tamoxifen might be useful to modulate vascular tone in a patient having compromised vascular tissue. In addition, libido and erectile function are very different conditions, as described above. As such, a person of ordinary skill in the art reading the Delaney *et al.* reference would not have been motivated to use tamoxifen to modulate vascular tone in such a patient, or to modulate penile vascular tone in a mammal in need thereof.

The Zhang *et al.* reference and the Drug Facts and Comparisons reference fail to remedy the deficiencies of the Delaney *et al.* reference. At no point do either of these references suggest that a chloride channel blocking agent such as tamoxifen would be useful either to modulate

vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction or to modulate penile vascular tone in a mammal in need thereof. Moreover, at no point does the combination of the Delaney *et al.* reference with the Zhang *et al.* reference and the Drug Facts and Comparisons reference suggest that a chloride channel blocker would be useful to modulate vascular tone either alone or in combination with another agent (e.g., a vasodilator), no matter how it was administered. Thus, the combination of these three references fails to render claims 31, 32, and 38 obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 31, 32, and 38 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 22-24, 27-29, 31-35, and 38-43 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: November 2, 2004

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